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THE PREBIOTIC SYNTHESIS OF N^6-METHYLADENINE, 1-METHYLADENINE AND 1-METHYLHYPOXANTHINE

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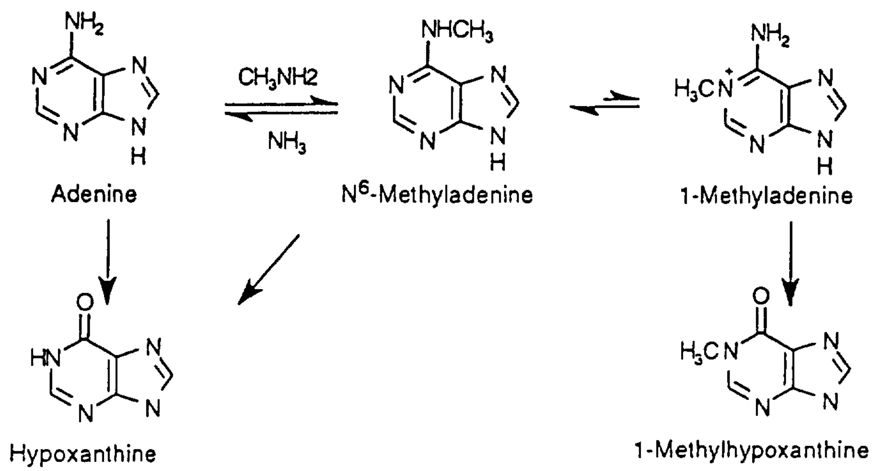
The methyl subtituted purines N^6-methyladenine and 1-methyladenine occur in modern tRNA and rRNA. This suggests that they may have been important in an earlier period in evolution, such as the RNA world, where they may have been involved in catalytic activity of ribozymes or in storing genetic information. N^6-Methyladenine has been shown to prevent triple strand formation of polynucleotides (Griffin *et al.*, 1964; Ikeda *et al.*, 1970). This base may therefore have played an important role in early replication systems. 1-Methylhypoxanthine and N^6,N^6-dimethyladenine are also found in tRNA.

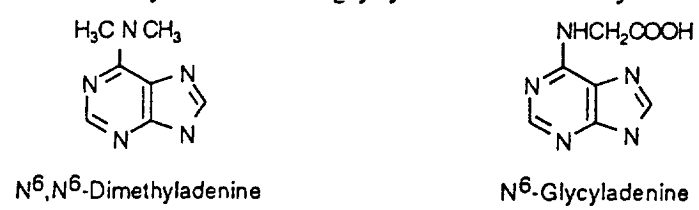
Although the prebiotic synthesis of purines is well established (Oró, 1961; Ferris *et al.*, 1968), there has been no reported prebiotic synthesis of the methylated purines. We have been able synthesize N^6-methyladenine, 1-methyladenine and 1-methylhypoxanthine by the reaction of adenine with methylamine. Methylamine is likely a prebiotic compound that occurs in the Muchison meteorite (Jungclaus *et al.*, 1976). Methylammonium chloride is a very soluble compound (21.5 molal at 25°C) compared to ammonium chloride (7.5 molal at 25°C). These high concentrations can be achieved using an evaporating lagoon or dry beach model of prebiotic synthesis (Robertson and Miller, 1995a). Yields as high as 50% have been obtained for the synthesis of N^6-methyladenine from solutions containing adenine and 20 molal $CH_3NH_2/CH_3NH_3^+$ buffer at pH 8.6 and 100°C. The rate of reaction is proportional to the mole fraction of methylamine. Reaction rates for a solution of adenine and 5.2 molal $CH_3NH_2/CH_3NH_3^+$ buffer were measured at different temperatures. The rate at pH 8 and 100°C, was determined to be 8.8×10^{-7} s^{-1} ($t_{1/2} = 9$ days) and $\Delta H = 28$ kcal.

The prebiotic synthesis of 1-methyladenine follows from that of N^6-methyladenine by means of a Dimroth rearangement. The equilibrium favors N^6-methyladenine with $K_{eq} = [m^6A]/[m^1A] = 690$ at pH 8 and 100°C as determined by direct measurement. The rate of formation of 1-methyladenine is $2.7 \times 10^{-7} s^{-1}$ ($t_{1/2} = 29$ days) under these same conditions.

1-Methyladenine hydrolyzes to 1-methylhypoxanthine. The prebiotic synthesis of N^6-methyladenine therefore yields 1-methylhypoxanthine as well. Hypoxanthine is formed from the hydrolysis of both adenine and N^6-methyladenine.



Similar reactions occur with other amines. A mixture of 3M dimethylamine and adenine at pH 8.9 and 100°C was found to yield 1.5% N[6],N[6]-dimethyladenine in 84 days. A mixture of 2M glycine pH 8 and 100°C was found to yield 44% N[6]-glycyladeninine 42 days.



These findings suggest that there was a greater variety of purines available on the primitive Earth than previously thought, as has been shown with the pyrimidines (Robertson and Miller, 1995b). Given the proper conditions N[6]-methyladenine may have been present in significant amounts relative to adenine with smaller amounts of 1-methyladenine and 1-methylhypoxanthine. N[6],N[6]-Dimethyladenine and other substituted adenines would also have been present. Methylated adenines, like adenine itself, may therefore have played an important role in the RNA world.

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De Graaf, R.M. et al.: 19
Cooper, G.W. et al.: 199